Pre-Conference Workshop
Toxicological risk assessment for early medicines development: case studies & discussion

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**Outline**

- Early compound characterisation
- Key objectives of preclinical safety programme
- Minimum (typical) preclinical package to enable FIH studies
- Example: CNS Drugs
- Example: Interpretation of equivocal findings
- Resources and communication
- Possible outcomes and success rates
- Conclusions and take home messages
Outline

Early compound characterisation

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Resources and communication

Possible outcomes and success rates

Conclusions and take home messages
Early compound characterisation

Screening strategies to select most promising candidates

In silico (computational)

Physical screening (miniaturised formats)

Capturing many features of classes of molecules and of individual representatives

Should select the most promising candidates
RISK: Drug and/or target promiscuity

Aim: assess binding affinity and functional activity at unintended targets (“off-target”)

- More recent approach: Computational prediction
- Drug and target promiscuity
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Key objectives

- Identify initial safe starting dose and subsequent dose escalation schemes in humans
- Identify potential target organ toxicity incl. dose dependence, relation to exposure and where appropriate, reversibility
- Identify safety parameters for clinical monitoring
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Minimum requirements

- General toxicity studies in rodent and non-rodent
- Genetic toxicology
- Safety pharmacology
Key parameters in safety assessment

- **SR** (Safety Ratio)
- **NO(A)EL** (No observed adverse effect level)
- **MTD** (Maximum tolerated dose)

Other parameters may be more appropriate to set starting dose in humans (e.g. MABEL)
Safety Ratio (SR) – multiples of exposure

Parameter to estimate relative safety

- Usually based on AUC
- However, Cmax may be more relevant (CNS/CVS)

Comparison of systemic drug exposures

- In patients at therapeutic doses up to the maximum recommended human dose (MRHD)
- With those in animals at the no-observed-adverse-effect level (NO[A]EL)

For NCEs

- SRs (i.e. multiples of exposures at NOAEL) normally at least 20
- but SRs may even be less than 1
NOAEL = No Observed Adverse Effect Level

Toxicities in the animals may depress the NOAEL

- dose level at which no adverse effects were observed

Room for interpretation
- What is considered adverse?

Altered SRs may result from

Changes in NOAEL

Changes in human exposure
MTD = maximum tolerated dose is a function of

- Study type
- Regulatory region
- Duration of dosing
- Species
Study type and regulatory region

- Reprotox
- Carcinogenicity
- Juvenile tox (US)
- Genetic tox

Relative degree of toxicity considered to establish MTD

1 5 10

Japan US EU

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Safety pharmacology

Investigate effects on **vital functions**

| Cardiovascular | Respiratory | Central nervous systems |

Core battery of tests

Any follow-up/supplemental studies based on cause for concern
General toxicology

Key elements

- Selection of relevant species
- Dose range finding studies (non-GLP)
- Pivotal GLP studies
Dose range finding (DRF) studies

Objectives

Identify Maximum tolerated dose (MTD) for main studies

Not uncommon to see mortality at doses > MTD

Particularly for CNS, CVS or other drugs targeting vital functions for which the prevailing findings are dominated by exaggerated pharmacological effects.
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Example: CNS active drugs

Patient tolerance for CNS effects may be greater than that of (healthy) animals and healthy volunteers.

Many CNS drugs in clinical use but also other medicines have low safety margins (if any) based on adverse preclinical findings.
Low safety margins – typical causes

**Clinical (in-life) intolerance**

- e.g. CNS clinical signs in one or more laboratory species (rat, dog, non-human primate, rabbit etc.) often consistent with exaggerated pharmacology

**Target-organ toxicity**

- e.g. liver, kidney, lungs, CNS, eyes, endocrine (e.g. (pituitary) and cardiovascular systems (heart, blood vessels) etc. consistent with on and/or off-target effects
Clinical intolerance - typical profile

Steep dose-response

CNS-symptoms
- Such as tremor, altered activity, altered posture, ataxia, recumbency etc., reduced body temperature (rodent), convulsions at high(er) doses
- Typically transient and reversible
- Often strong correlation with systemic Cmax

Mortality may be seen at low multiple of those doses with first mild CNS signs
- May even occur at doses only 2-3 fold the NOAEL and/or MRHD (based on HED = human equivalent dose on mg/m² basis)

No histopathological findings in the brain
Typical features of target organ toxicity

CNS active drugs must be able to pass the blood-brain barrier

Physico-chemically characterised by high(er) lipophilicity

May undergo extensive metabolism

Rodents may show greater clinical tolerance
  • Identification of target organs other than CNS more likely in these species

Doses in non-rodents not uncommonly limited by clinical tolerance

May therefore adversely affect any other organ system in the body
Exceptional changes

Adverse CNS effects are commonly

- Functional
- Not morphological

Morphological alterations in the brain

- Exceptional

Observed e.g. for drugs interacting with the NMDA receptor such as

- Phencyclidine (PCP) (Olney, Science 1989)
  - «Angel Dust»
  - «Olney’s lesions» – neuronal vacuolation

- MK-801 (Auer, Stroke 1996)

- Memantine (Creeley, Neurobiology of Aging 2008)
Drugs causing morphological findings in the brain

Mostly not marketed

Impossible to monitor in the clinic

Unless perhaps if they were reliably identifiable by a biomarker indicating a fully reversible functional stage well preceding any changes at the histopathological level

• How to identify?
• How to translate from animals to humans?
• Safety margins?

Virtually impossible to ascertain patient safety
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Interpretation?

Is there cause for concern?

Based on which observations?

Can this be answered?

Approach?
Mortality – end of story?

Not necessarily - principle of Paracelsus does apply!

Interpretation of other findings at dose levels > MTD?

Consistent with mode of action?

Consistent with kinetic profile?

Coherent between species?

Any (apparent) species differences?

Functional effects only?

Morphological changes?

Adverse?

Individuals affected or dose-related increase in incidence and severity?

If individuals only – context?
Issue identified - stop development?

Not immediately!

Address observation to establish answers to the following questions:

- Real observation or artefact?
- Nature of observation?
- Exacerbation of spontaneous finding?
- Known class finding?
- Individuals only affected?
  - Could it be a chance finding?
  - Outlier?
  - Or is it representative for the group?
- Specifically susceptible?
- Is more than one species affected?
- Signal for same organ system in other studies?
- Strength of signal?
What are the (predicted) safety margins?

Are the safety margins a reliable tool to estimate/mitigate and/or manage human risk or do additional factors have to be taken into account?

Could the finding be species-specific?
- Does species-specificity truly mean a difference in specificity or rather sensitivity?
- If the latter – are humans less sensitive? If so, how much?
- Can this be answered at all?
Issue identified - stop development?(3)

- Is the observation reversible?
- Does the finding deteriorate with ongoing treatment – perhaps to an irreversible stage?
- What is the degree of severity?
- Finding monitorable in the clinic?
- Finding considered predictive or relevant for humans?
- Can this question be answered at all (at this stage)?
Question to be answered

Is there cause for concern?

(all/any of) these points?

Can we answer

If yes...

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Some thoughts

Sponsor taking overall responsibility of a given programme

- Responsible toxicologist – study monitor
- A senior supervisor
- Project teams composed of experts from all disciplines involved
- Management

Experts involved in a single study

- Study director
- Technicians to support all investigations
  - including clinical observations, body weight, food consumption, blood samples for TK, clinical biochemistry, haematology, ECGs, ophthalmoscopy, necropsy, macroscopy
- Pathologist to undertake histopathological assessment of a full list of tissues
- Peer review of pathology phase

Minimum package of a total of about 10 studies to be assembled

- All in one place? Several test facilities/test sites (CRO/Sponsor) involved?
Objectives of preclinical risk assessment

- All data need to be interpreted and overall pattern needs to be integrated
- To identify concerns across studies
- Put findings into context
- To support risk-benefit assessment
Which support could help achieving these?

Communication across disciplines

• Key requirement to support this process effectively

Helpful approaches may include – but not be limited to –

• Critical assessment of findings across all studies to integrate information
• Independent pathological peer review across studies
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Final aim for any assessment

Beware: Testing concepts current at a given point in time determine resulting testing strategies!

Transform information into knowledge
Limitations

<table>
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<tr>
<th>If medical and/or scientific concepts are hampered by (intrinsic?) limitations the resulting testing strategies may be deficient</th>
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<tbody>
<tr>
<td>Such situations limit our understanding at a given point in time</td>
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<tr>
<td>Our apparent knowledge of today might be our potential errors of tomorrow</td>
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<tr>
<td>We should expect the unexpected at all times</td>
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Approximately 60% of compounds are terminated before entering phase I trials due to unfavourable risk/benefit profiles. Processes therefore work reasonably effectively with a remaining proportion being missed due to...

- Increasing doses in clinical development which in turn reduce safety margins and modify risks/benefit profile
- Certain endpoints typically not assessed before phase I
- Adverse effects becoming evident upon prolonged treatment
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Conclusions

There is a potential gap between information and knowledge

Identification of such gaps might not be straightforward

There is always a risk of failure

Timely communication between all disciplines involved is mandatory to support successful medicine development

Preclinical and clinical development remain closely intertwined from start to end

Ongoing risk assessments should be undertaken to integrate all data as they become available, including from other sources, such as from the public domain
Take home message

Expect the unexpected at all times!
Thank you very much for your attention!
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Further reading (selection)
